REMARKS / ARGUMENTS

1. No New Matter Has Been Added

No new matter has been introduced by way of this amendment. For each amendment made, proper support exists in the originally filed specification at the pages indicated.

2. Summary of Amendments

Independent claim 101 has been amended to specify that the device is a "solid phase microextraction" sampling device; to indicate that the coated end of the fibre is for positioning within "a blood vessel", and to state "wherein said fibre is a flexible wire".

No change has been made to dependent claims 102 - 107. 109, or 118 - 119.

3. Support for Amendments Within Specification

The limitation of "solid phase microextraction", also referred to interchangeably throughout the description as "SPME", can be found throughout the specification, including both the background and detailed description sections, examples of which are provided below:

> Newer approaches that extend the applicability of conventional SPME technology, where an externally coated extraction phase on a micro fibre is used, seem to be logical targets for the development of such tools.
>
> (page 3, lines 11-12)

> With the current commercially available SPME devices a stationary extraction polymer is coated onto a fused silica fibre.
>
> (page 3, lines 11-12)

> To date commercial SPME devices have been used in some applications of direct analysis of living systems.
>
> (page 3, lines 22-23)

> Also the present SPME devices cannot be conveniently coupled to positioning devices necessary for in-vivo investigation at a well-defined part of the living system.
>
> (page 4, lines 12-14)

> Up to now SPME devices have been designed to be re-used numerous times. While it is possible to re-use the polypyrrole coated fibre (wire) device described above, it is advantageous that this device be employed as a single-use device.
>
> (page 22, lines 4-6)

> The desorption solvent (2 ul) was placed on the surface of the SPME fiber coating.

(page 42, lines 14-15)

> One of the methods is to deliver the calibration compound by utilizing SPME fibre to the analytical instrument.

(page 45, lines 4-5)

The limitation of positioning within "a blood vessel" has been added to claim 1, and is supported throughout the specification and claims as filed, for example at the passages indicated below:

> The positioning device itself may a catheter, for those applications where the fibre is guided into a blood vessel, such as a vein, or other tubular biological structures, as discussed in more detail below.

(page 12, lines 4-6)

> It will follow curves in a vein or catheter and normally resume a straight configuration when removed.

(page 16, lines 26-27)

> Figure 1, part C, illustrates an embodiment comprising the extraction device alone with no support rod and no handle may be introduced to a blood vessel through a previously placed medical catheter 10 with attached PRN 12.

(page 17, lines 6 to 8)

> 9. The method of any one of claims 1 to 7, wherein said fibre is positioned within a blood vessel, and wherein said one or more component of interest is adsorbed from blood flowing through said blood vessel.

(original claim 9 as filed, see page 58 of specification as filed)

The limitation of the fibre being "a flexible wire" has been added to claim 1, and is supported throughout the specification, for example at the passages indicated below:

> The extraction phase 4 could be a polymeric layer prepared on the wire surface, particulate adsorptive or absorptive material glued or otherwise affixed to the wire surface, or immobilized biorecognition agents such as antibodies nucleotides or protein receptors. When constructed of the stainless steel wire described below the extraction device is quite flexible. It will follow curves in a vein or catheter and normally resume a straight configuration when removed.

(page 16, lines 22-27, with reference to Figure 1)

> Optionally, the fibre diameter can be of millimeter to nanometer dimensions, and formed of any acceptable material that would be amenable for use in the intended application. Such materials may include fused silica, plastic, carbon or metal wire.

(page 11, lines 3-5)

> A device for in vivo study of chemical concentrations consists of a fibre or wire and associated extraction phase. The fibre or wire may be made of fused silica, metal, carbon, graphite or a polymeric material.

(page 13, lines 20-22)

> As an example of an extraction phase, polypyrrole may be deposited onto the surface of a fine metal wire by electrolytic oxidation under conditions of controlled potential The polymer can be prepared on thin stainless steel wire as described below.
>
> (page 17, lines 27 to 30)

5. Claim Rejections - 35 USC §102

That Applicant believes that the claim rejections raised on pages 3 to 4 under 35 USC §102 are traversed by the amendments and arguments in support thereof now put forward. The amendments made to claim 101 emphasize features that are not taught or suggested in any prior art reference, or specifically in the Pompidou et al reference (U.S. 6,689,603). Each of the remaining claims depends from claim 101, and thus each dependent claim also overcomes the objection raised under 35 USC §102, as well as the objections raised under §103, addressed separately below.

The Pompidou et al. reference relates to a device that can be used to insert a support into a biological sample or system, on an investigational microsystem is attached. In the passage the examiner refers to on page 4 of the action, where a coated end comprises antibodies as an extraction phase, there is no alternative suggesting that instead of antibodies, an SPME extraction phase be used. The microsystem of Pompidou et al. may include an array of biological molecules, or "reagents" such as ligands (antigens or antibodies), but nowhere in the document is SPME suggested. The Examiner's attention is drawing to the following passages of Pompidou et al.:

> Investigation microsystems employing an array of biological molecules placed in given positions on a surface are described in the prior art. Those systems, known as "biochips" or DNA chips, are useful for the investigation of polynucleotide or amino acid sequences. Examples of such systems are described, for example, in the European patent applications published under No. 619,321, No. 373,203 and No. 691,978. Other investigation microsystems are, for example, the microanalysis tests using ligand/receptor type reactions or microimmunoanalyses using antigen/antibody type reactions.
>
> (col. 1, lines 13-23)

> Within the scope of the therapeutic applications, the biological and/or chemical substances arrayed in each predefined region of the surface of the microsystem are active agents, notably therapeutic substances. The active agents can be any substance useful in the treatment of diseases requiring an intervention in target cells or tissues, like cancer cells, centers of infection, etc.
>
> (col 2, line 66 - col 3, line5)

> The microsystem according to the invention advantageously uses biological substances which are polynucleotide or amino acid sequences. The invention envisages as chemical or biological substances present in each predefined region chemical or biological substances constituting: an array of polynucleotide sequences capable of being hybridized with nucleic acids present in the substrate notably constituting the investigation site, or an array of peptides, polypeptides or proteins capable of reacting with a corresponding receptor or immunologically with antibodies or antigens present in the substrate notably constituting the investigation site.
>
> (col 3, lines 48-52)

Not only is it inappropriate to equate the microsystem/device of Pompidou with an SPME system using an extraction phase, but further limitations have been added to claim 101 that will distinguish over Pompidou et al. In particular, the final line of claim 101 now indicates that the fibre is a flexible wire, and the body of the claim clearly indicates throughout that insertion into a blood vessel is intended. A wire allows the flexibility of inserting the coated end (SPME extraction phase) via a catheter into a blood vessel. The device of Pompidou et al is too bulky to fit into a blood vessel, and does not incorporate a flexible wire. In fact, passages indicate that a rigid support of "several" cm^2 in surface area is required on which a biological array may be supported in the Pompidou et al. device. This rigid support not only renders the Pompidou et al device different from claim 101, but makes the device too rigid and bulky to fit into a blood vessel. By stipulating a wire, and indicating use within a blood vessel, claim 1 as amended overcomes the cited reference. Also, there is no rigid component required in claim 101, further distinguishing the device from that of Pompidou et al. The examiner's attention is drawn to the following passages of Pompidou et al.:

> FIG. 5 shows a pilot apparatus in which the rigid plastic support is inserted in the guidance system.
>
> (col 8, lines 56-57)

> The results obtained on this work show that it is possible (i) to fix on a rigid support (joined to a flexible rod) two antibodies of different specificities (anti-Candida and anti-laminin), (ii) to sample corresponding analytes (Candida and laminin antigens), and (iii) to identify those analytes by antibodies labeled with biotin which is then revealed by a streptavidin-enzyme complex.
>
> (col 9, lines 23-29)

> *Rigid plastic supports*
> Three types of plastic supports were chosen and used for development of the system, one described as "yellow" plastic, one described as "blue" plastic and one described as "white" plastic. For each, three methods of coupling were tested, as represented on the attached FIG.

4: coupling without treatment (.o slashed.), coupling with treatment by coupling agent 1 (A1), and coupling with treatment by coupling agent 2 (A2). The three types of support were tested untreated or treated with A1 or A2 and for each system the supports were used sensitized with the anti-M Ab (U). The "white" and "blue" supports gave similar results. Only the support consisting of "white" plastic, 2 cm long and treated with coupling agent A2, was adopted for continuation of the experiments.

(col 10, lines 17-32)

In a first embodiment, the microsystem is of the type comprising a support on the surface of which predefined regions are arrayed, each containing different chemical or biological substances for investigation or treatment of the substrate into which the microsystem is brought in contact thanks to the flexible rod. Said surface contains at least two and preferably more than 100 and especially preferably more than 1000 predefined regions on a surface in the order of several cm^2 and preferably in the order of 1 cm^2 or less. Each predefined area contains a different chemical or biological substance, but the process according to the invention also allows several or even all of said predefined regions to contain the same chemical or biological substance, for example, in case of the same analysis or of delivery of the same active substance in time.

The support can contain several faces, at least one of which consists of an active surface. The latter is the site of one or more biological bonding agents. In the midst of said active surface predefined regions are arrayed.

This surface of approximately one cm^2 can be flat and is situated in a single plane, and it can also be ribbon-shaped and spiral-wound on a rigid support which extends the flexible rod and then presents the microsystem of the same nature as the previous one, but of a more elaborate configuration. FIG. 1 represents a working example of an apparatus according to the invention, consisting of a flexible rod (1) like, for example, a deformable catheter, at the end of which the microsystem (2) is inserted in the opening of the flexible rod, the microsystem consisting of a support (3) on which a ribbon (4) is wound or specific antibodies of an antigen present in the substrate analyzed are fixed. ***The support (3) is rigid***, while the flexible rod (1) is relatively deformable. The flexible rod (1) can be combined with an endovascular exploration system (5) like, for example, an endoscope.

(col 1, line 60 - col 2, line 25)

For these reasons, it is believed that claim 101 is not anticipated or obvious in view of Pompidou et al.

6. Claim Rejections - 35 USC §103

That Applicant believes that the claim rejections raised on pages 4 to 9 under 35 USC §103 are traversed by the amendments and arguments in support thereof now put forward above. The amendments made to claim 101 emphasize features that are not taught or suggested in any prior art reference either alone or in combination with any other reference.

Objections were raised to claims 102, 103, 106, 109, and 119 on the ground that these claims are obvious when Pompidou et al. is considered in view of Gourley et al. (U.S. Patent 5,120,510). Gourley does not teach the limitations now included in claim 101 from which these claims depend, specifically, that the device is for SPME, that the fibre is a wire, and that the coated end of the fibre (wire) is for insertion into blood vessels. Thus, the combination of Pompidou et al. and Gourley et al. do not render these claims obvious.

An objections was raised to claim 104 on the ground that this claim is obvious when Pompidou et al. is considered in view of Colburn et al. (U.S. Patent Publication 2003/0183758). Colburn et al. does not teach the limitations now included in claim 101 from which claims 104 depends, specifically, that the device is for SPME, that the fibre is a wire, and that the coated end of the fibre (wire) is for insertion into blood vessels. Thus, the combination of Pompidou et al. and Colburn et al. do not render these claims obvious.

An objections was raised to claim 105 on the ground that this claim is obvious when Pompidou et al. is considered in view of Riviere et al. (U.S. Patent Publication 2003/0180954). Riviere et al. does not teach the limitations now included in claim 101 from which claims 105 depends, specifically, that the device is for SPME, that the fibre is a wire, and that the coated end of the fibre (wire) is for insertion into blood vessels. Thus, the combination of Pompidou et al. and Riviere et al. do not render these claims obvious.

Objections were raised to claims 107 and 118 on the ground that these claims are obvious when Pompidou et al. is considered in view of Pawliszyn (U.S. Patent 5,691,206). U.S. Patent

5,691,206 does not teach the limitations now included in claim 101 from which claims 107 and 118 depend, specifically, that the device is for SPME, that the fibre is a wire, and that the coated end of the fibre (wire) is for insertion into blood vessels. Thus, the combination of Pompidou et al. and U.S. Patent 5,691,206 do not render these claims obvious.

Each of these claims now depends from claim 101 as amended, which includes further limitations not found in any of the above-noted documents. Thus, the arguments put forward above with respect to claim 101 should be adequate to render other objections on the basis of obviousness moot. Full analysis of each objection, and why a prima facie case of obviousness has not been established are thus not included here. However, briefly, the applicant wishes to point out to the examiner the following differences between the applied art and the instant invention as now claimed in claim 101.

Regarding the Examiner's comments regarding a MALDI-related reference (Colburn at al.), although application of MALDI is common, the format of SPME-MALDI is unique since it incorporates the extraction step, among other distinctions now found in claim 104 as it depends from 101.

Regarding the calibration standard reference (Riviere at al), the use of calibration standards are common, the calibrant according to the embodiment of the invention claimed in claim 105 is delivered to the investigating system via the extraction phase, not by previous spike of the investigated system. This approach to calibration is compatible with in-vivo monitoring since only small amount of calibrant enters the investigated tissue rather then contamination of the whole investigated system. Riviere et al. measures permeation of a membrane, not the concentration of analytes.

The remaining references of Quay et al. and Basta do not teach or suggest the limitations now recited in the claims. It is believed that the obviousness objections raised to claims 102-103, 104, 106 and 108 are rendered moot and should thus be withdrawn.

Applicant believes that no fee is due with this submission, but nevertheless authorizes the Commissioner to debit any required fee from or credit any overpayment to Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP.

It is submitted that this application is in condition for allowance. Early and favorable consideration is respectfully requested.

Respectfully submitted,

Janusz B. PAWLISZYN

/Kathleen E. Marsman/
By: _____
Kathleen E. Marsman
Reg. No. 48,121
Borden Ladner Gervais LLP
World Exchange Plaza
100 Queen Street, Suite 1100
Ottawa, ON K1P 1J9
CANADA
Tel: (613) 787-3572
Fax: (613) 787-3558
E-mail: kmarsman@blgcanada.com

KEM